REMARKS/ARGUMENTS

Status of the Claims

Upon entry of the present amendment, claims 17-42 and 50-63 are pending. Claims 43-49 are canceled without disclaimer or prejudice to renewal. Claims 58-60 are withdrawn as directed to a non-elected invention. Claims 17, 23, 25, 31, 36, 37, 50, 52, 58 and 61 are amended. Claims 17, 25, 37, 50, 58 and 61 are amended to set forth the elected sequences, SEQ ID NO:7 and SEQ ID NO:16, and recite the variant amino acid sequences in the VL chain CDR1 and the VH chain CDR3. Support is found, for example, in paragraphs [0045-0053]. Claims 23, 31 and 52 are amended to remove language referencing Figures 2 and 3. Claim 36 is amended to track the language of claim 35 for proper antecedent basis.

No new matter is added by the present amendments, and the Examiner is requested to enter them.

Amendments to the Specification

Applicants provide with this response a Substitute Sequence Listing, correcting the sequences of SEQ ID NOs:15-19. In particular, the 2nd amino acid of the heavy chain CDR3 is corrected to be an Arginine residue and not a Phenylalanine residue. The description in paragraph <223> for SEQ ID NO:15 is also corrected to reflect that the sequence is a heavy chain CDR3, and not a heavy chain CDR2. Support is found, for example, in Figures 1 and 3, and in SEQ ID NO:21 of the present application. Support is also found in Figure 1 of Mansfield, *et al.*, *Blood* (1997) 90:2020, a copy of which is provided with this response as Exhibit A.

This amendment is accompanied by the Substitute Sequence Listing in computer readable form, and a paper copy of the sequence information which has been printed from the computer readable form. The information contained in the computer readable form was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. No new matter is added by the present amendments to the sequence listing.

Claim Objections

The Examiner objects to claims 23, 31 and 52 for referencing Figures 2 and 3. In response, Applicants have amended claims 23, 31 and 52 to remove language referencing Figures 2 and 3.

The Examiner objects to the phrase "at a position corresponding to position 490 of SEQ ID NO:24." Applicants respectfully point out that this language is clear, concise and correct. As discussed in paragraph [0066] on page 19 of the specification, the positions in *Pseudomonas* exotoxin (PE) and its variants are described by those of skill with reference to the sequence of the native PE molecule. Therefore, the position may not be actual position 490 in the PE variant, but it will correspond to position 490 in the native PE molecule, the sequence of which is provided as SEQ ID NO:24. For example, SEQ ID NO:23 provides the sequence of the PE variant "PE38," wherein the Arg residue corresponding to position 490 of the native PE molecule is mutated to an Ala residue. In the PE38 variant, the actual position is 222. Accordingly, Applicants respectfully submit that language referencing the positions of the native PE molecule is clear to those of skill in the art and is proper in the claims.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 35, 36, 41, 42, 56 and 57 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

A) The Examiner rejects claims 35, 41, 42, 56 and 57 for recitation of the names of the PE variants. The PE variants are described in the application and were known in the art at the time of filing the present application. The structural landscape of the native PE molecule is described in paragraph [0156] on page 42. This paragraph summarizes the residues comprising the different domains of the native PE molecule, published as SEQ ID NO:1 in U.S. Patent No. 5,602,095 and provided as SEQ ID NO:24 in the present application. The positions of the amino acid residues are with respect to the native PE molecule, or SEQ ID NO:24.

Variant PE4E is described in paragraph [0158] of the present specification. In variant PE4E, the basic residues of Domain Ia positions 57, 246, 247 and 249 of the native PE molecule are replaced with acidic residues (*e.g.*, glutamic acid or "E").

Variants PE40 and PE35 are described in paragraph [0159] of the present specification. In variant PE40, the residues of Domain Ia, residues 1-252, are removed. In variant PE35, amino acids 1-279 and 365-380 of the native PE have been deleted. Copies of references Pai, *et al.*, *Proc Natl Acad Sci* (1991) 88:3358 and Kondo, *et al.*, *J Biol Chem* (1988) 263:9470 are provided as Exhibits B and C. PE35 and PE 40 are also described in U.S. Patent Nos. 5,602,095 and 4,892,827.

Variant PE38 is described in paragraph [0160] of the present specification. PE 38 is a truncated PE pro-protein composed of PE amino acid residues 253-364 and 381-613, and is publicly described, *e.g.*, in U.S. Patent No. 5,608,039. The PE KDEL variants, including PE38KDEL, contain an endoplasmic reticulum retention signal sequence at the C-terminus, as described, *e.g.*, in paragraphs [0016], [0157] and [0160-0161].

PE38QQR is a truncated form of PE composed of amino acids 253-364 and 381-608. The lysine residues at positions 509 and 606 are replaced by glutamine and at 613 are replaced by arginine. PE38QQR is described in Debinski *et al.*, *Bioconj. Chem.* (1994) 5:40, attached as Exhibit D.

B) The Examiner rejected claim 36 for insufficient antecedent basis. In response, Applicants have amended claim 36 to depend from and track the language of claim 35 for proper antecedent basis.

Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 35, 36, 41, 42, 56 and 57 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not complying with the enablement requirement. Applicants respectfully traverse for the reasons discussed below.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *See*, M.P.E.P. § 2164.01, *citing United States v. Telectronics, Inc.*,857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367,

1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). *See also In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Here, the rejected claims recite in Markush language specific PE mutants that were known in the art prior to the filing of the present application. Publications describing the specific PE mutants recited in the claims are discussed above and in the specification, *e.g.*, at paragraphs [0157-0161]. The listed mutants refer to particular, known species of PE mutants. Also, the specification describes the convention of referencing amino acid residue positions of PE molecules with respect to the native PE molecule, provided as SEQ ID NO:24 in the present application. The claims recite mutating one amino acid at a particular amino acid position that corresponds to arginine at position 490 of SEQ ID NO:24, and the particular amino acid residues that are substituted at this position. Therefore, the claims are directed to mutating one specifically identified position, not general sequence variation. The mutated position is in the same structural region of all the PE mutants, because they are mutated at the arginine position corresponding to position 490 of the native PE.

Accordingly, based on what was already known in the art regarding the PE mutants and what is taught in the specification, those of skill could readily determine the position in the listed prior known mutant PE molecules that corresponds to arginine at position 490 in the native PE molecule, and substitute one of the listed amino acid residues for the arginine, as claimed. Moreover, Applicants respectfully point out that the rejected claims are all dependent claims, reciting prior known PE mutants. The patentability of the present invention does not rely on the subject matter recited in claims 35-36, 41-42 and 56-57. The present rejection does not include any of independent claims 25, 37 or 50.

Because the person of ordinary skill could make and use the PE mutants without undue experimentation and with a reasonable expectation of success, Applicants respectfully submit that claims 35-36, 41-42 and 56-57 are enabled. Reconsideration is respectfully requested.

Request for Rejoinder Pursuant to M.P.E.P. § 821.04

Claims 58-60 are withdrawn from examination as being drawn to a non-elected invention. Claims 17-24 and 58-60 are related as composition and methods of use. Upon entry of the present amendments, Applicants believe that composition claims 17-24 are allowable. Accordingly, pursuant to M.P.E.P. § 821.04, Applicants respectfully request withdrawal of the restriction requirement with respect to composition claims 17-24, and method claims 58-60, and examination of the withdrawn methods of use claims. In accordance with M.P.E.P. § 821.04, the scope of claims 58-60 corresponds to claim 17.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 20-1430.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Jennifer L. Wahlsten
Reg. No. 46,226

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
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